REMARKS

I. Status of the Claims

Claims 1-17 are currently pending and claims 12-17 are currently withdrawn in this application. With entry of this amendment, claims 2, 3, 9 and 11 will be amended, and claim 18 will be added. The amendment to claims 2 and 3 corrects for formal matters only. Support for the amendment to claim 9 can be found in the specification as filed on page 10, lines 4-14. Support for the amendment to claim 11 can be found in the specification as filed on page 10, lines 26-29 and page 13, lines 16-22. Support for new claim 18 can be found in the specification at page 10, lines 26-28. No new matter has been added by way of these amendments.

With entry of this amendment, claims 1-18 will be pending.

II. Election/Restriction

Applicants thank the Examiner for acknowledging withdrawal of the species election restriction requirement indicated in the Office Action of November 2, 2005.

III. Claim Objections: Duplicate Claims

The Examiner contends that should claim 3 be found allowable, claim 4 will be objected to as being a substantial duplicate thereof. Additionally, the Examiner contends that should claim 5 be found allowable, claims 6 and 7 will be objected to as being substantial duplicates thereof.

Applicants respectfully submit that claim 4 is not the substantial duplicate of claim 3 because claim 3 recites any AAV vector cell strain wherein the cell is a BHK-21 cell whereas claim 4 sets forth the specific cell strain, BHK/HO-1. Similarly, claims 6 and 7 are not substantial duplicates of claim 5 because claim 5 recites any recombinant viral vector made from pSNAV1/HO-1 whereas claim 6 sets forth a recombinant viral vector produced from a cell strain containing pSNAV1-HO-1 and claim 7 recites a recombinant viral vector produced from the

specific cell strain, BHK/HO-1. Thus, claims 4, 6 and 7 cover subject matter distinguishable from each other and from the claims from which they depend.

Accordingly, applicants respectfully request that the Examiner withdraw these objections.

IV. Claim Rejections: Enablement - Biological Deposit

Claims 1-10 stand rejected as not enabled. The Examiner contends that the specification does not enable a person skilled in the art to obtain the recombinant virus, HSV1-rc, or the plasmid, pSNAV1/HO-1, without undue experimentation. The Examiner indicates that the rejection can be overcome by showing that these biological materials are known and readily available to the public or by depositing these materials with an International Depository Authority (IDA).

Applicants traverse these rejections.

As described in the specification, recombinant virus HSVI-rc was a known and readily available biological material as described in Chinese patent application No. 98120033.8, published on February 9, 2000 with the publication No. CN1248627A, and granted on May 28, 2003 with the publication No. CN1109754C (specification, p. 10, ll. 10-12) (English translation of CN1248627A attached as **Exhibit A**). Accordingly, one of ordinary skill in the art at the time of the invention would be enabled to make and use the known and readily available recombinant virus HSVI-rc.

As described in the specification, applicants note that plasmid SNAV1/HO-1 was constructed from rat HO-1 gene and the key vector pSNAV1, and that both rat HO-1 gene and the key vector pSNAV1 were known and readily available to the public at the time of the invention (specification, p. 9, ll. 24-30; *see* Fig. 6). The key vector pSNAV1 was also described in Chinese patent application No. 99119038.6, published on May 10, 2000 with the publication No. CN1252450, and granted on June 15, 2006 with the publication No. CN1206361C (English translation of CN1252450 attached as **Exhibit B**). Cloning rat HO-1 was also described, for example, as early as 1985 in Shibahara S, et al., *Cloning and expression of cDNA for rat heme*

oxygenase, PROC. NAT'L. ACAD. SCI. U.S.A., 82:7865-69 (1985) (attached as **Exhibit C**). Thus, because both the rat HO-1 gene and the key vector pSNAV1 are described in the specification and were known and readily available to the public, one of ordinary skill in the art at the time of invention would have been enabled to make and use the construction of pSNAV1/HO-1.

In particular, "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Further, in the field of biology "a *considerable* amount of experimentation is permissible." *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (emphasis added). Thus, applicants submit that the component parts of the presently claimed invention were known and readily available at the time of the invention such that, given the disclosure provided in the specification, particularly at page 10, lines 10-12 and page 9, lines 24-30, those of ordinary skill in the art would have been enabled to make and use applicants' presently claimed invention without undue experimentation.

Applicants respectfully request that these rejections be withdrawn.

V. Claim Rejections: Indefiniteness

Claim 11 stands rejected for indefiniteness for failing to particularly point out and distinctly claim the subject matter which the applicants regards as their invention. Specifically, the Examiner contends that it is not clear whether mediation of the expression of the HO-1 gene entails increasing, decreasing, or altering the expression of the HO-1 gene and whether administration is to a patient, a cell, or tissue *in vitro*.

While not conceding as to the correctness of the Examiner's contention, Applicants respectfully submit that claim 11 has been amended in accordance with the Examiner's comments,

thereby replacing "mediating" with "providing for increasing" and specifying that administration is *in situ*. By these amendments, applicants submit that the rejection has been obviated and, accordingly, request its withdrawal.

VI. Claim Rejections: Enablement

Claims 9 and 11 stand rejected as not enabled. Regarding claim 9, the Examiner contends that the specification does not enable recombinant AAV virus production in all host cells both *in vitro* and *in vivo*. Regarding claim 11, the Examiner asserts that the specification does not enable all forms of mediating (*e.g.*, increasing and decreasing) HO-1 expression under all conditions by administering any effective amount of any recombinant AAV virus, including an AAV virus without an HO-1 gene.

Applicants respectfully traverse these rejections.

A. Claim 9

Applicants have amended claim 9 to specify that the production of recombinant AAV viruses occurs in hosts cells *in vitro*. Applicants submit that recitation of a particular *in vitro* host is not required because the specification enables the use of any host capable of producing a recombinant AAV virus.

To this end, the specification provides guidance on how to produce a recombinant AAV virus in host cells. Specifically, production of a recombinant AAV virus in a BHK-21 cell *in vitro* by transfecting the cell with pSNAV1/HO-1 and infecting the cell with rHSV1-rc is disclosed (*see* specification, p. 10, ll. 4-14). The specification also discloses how to purify the resulting recombinant virus and determine the titers for the virus using dot hybridization and flow cytometric techniques (*see* specification, p. 10, ll. 14-16). Thus, it would have been merely routine experimentation to replace BHK-21 cells with different cells in the above protocol and test for cells that can produce a recombinant AAV virus at the time of the invention.

Regarding the Examiner's contention that the specification does not support claims to a genus of host cells, applicants respectfully submit that the disclosure in the specification enables host cells in addition to the BHK-21 cells discussed above, and that "the law makes clear that the specification need teach only one mode of making and using a claimed composition" *Amgen Inc. v. Hoeschst Marion Roussel, Inc.*, 314 F.3d 1313, 65 U.S.P.Q.2d 1385 (Fed. Cir. 2003) (internal citation omitted). Regarding the enablement of alternative host cells, the Court of Appeals for the Federal Circuit in *In re Wands* acknowledged that in the field of biology "a *considerable* amount of experimentation is permissible" and, further, that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening" 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (emphasis added). Accordingly, applicants submit that utilization of any host cell for the *in vitro* production of AAV and replication of HSV helper virus would have been routine matter of reasonable experimentation by one having ordinary skill in the art at the time of the invention, such that amended claim 9 is enabled.

Applicants respectfully request that these rejections be withdrawn.

B. Claim 11

Applicants have amended claim 11 by replacing "mediating" with "providing for increasing," specifying that administration is via the direct *in situ* perfusion of an organ, and reciting that the recombinant viral vector comprises the HO-1 gene. Additionally, claim 11 has been amended to recite that "an effective amount" of recombinant AAV virus is "the amount required to increase carboxyhemoglobin in the peripheral blood of the animal transplanted with the perfused organ compared to carboxyhemoglobin in the peripheral blood of an animal not transplanted with the perfused organ." This procedure for determining the "effective amount" is described in the specification as filed, *e.g.*, on page 13, lines 16-22 and in Figure 1g.

Applicants further submit that the Examiner's reliance on two articles, Verma et al., NATURE 1997, 389:239-242 ("Verma") and Pfeifer et al., ANNU. REV. GENOMICS HUM. GENET. 2001, 2:177-211 ("Pfeifer"), on page 8 of the Office Action to support the contention that the state

of the prior art suggests "vector targeting *in vivo* to be unpredictable and inefficient" is inapplicable to the presently claimed invention. First, applicants note that Verma was published in 1997, 6 years prior to the filing the application for the present invention; thus, Verma is not representative of the state of the art at the time of invention. Second, as recited in amended claim 11 and as described on page 10, lines 26-29, the viral vectors of the present invention are delivered directly to the organ of interest using *in situ* perfusion, a method not disclosed or suggested by either Verma or Pfeifer. Accordingly, the Examiner's concerns of unpredictability and inefficiency are not applicable to amended claim 11.

In view of the above amendments and remarks, applicants respectfully submit that claim 11 is enabled and, thus, request that these rejections be withdrawn.

VII. Claim Rejections: Anticipation

A. Tsui

Claims 1-10 stand rejected as anticipated under 35 U.S.C. § 102(a) by Tsui et al. (CIRCULATION 2003, 107:2623-2629) (Tsui) because the present invention is published in Tsui as indicated on page 7, lines 3-5 of the application as filed.

Applicants respectfully traverse these rejections.

According to 35 U.S.C. § 102(a), applicants' disclosure of their own work within one year before the application filing date cannot be used against them. Accordingly, a declaration by the inventors under 37 C.F.R. § 1.132 is filed herewith stating that they are the authors of Tsui, an article published within one year before the application filing date (*see* declaration attached as **Exhibit D**). In the declaration the inventors, Tung-Yu Tsui and Xiaobing Wu, state that they conceived of the invention whereas the other authors of the Tsui article (*i.e.*, Chi-Keung Lau, David W.Y. Ho, Tao Xu, Yeung-Tung Siu, and Sheung-Tat Fan) did not participate in nor contribute to this conception. Accordingly, these other authors are not inventors of the presently claimed subject matter.

In view of the above statements and the newly submitted declaration, applicants respectfully request that these rejections be withdrawn.

B. Dzau

Claims 1, 5-8 and 11 stand rejected as anticipated under 35 U.S.C § 102(b) by Dzau et al. (U.S. Application Publication No. 2003/0022870) (Dzau) because every element of the AAV/HO-1 portion of the recombinant plasmid vector, pSNAV1/HO-1, is disclosed in Dzau and because Dzau teaches recombinant AAV viral particles carrying the HO-1 gene that can be administered.

Applicants respectfully traverse these rejections.

Applicants submit that Dzau does not disclose nor suggest all of the claim elements of independent claims 1 and 11. Claim 1 and dependent claims 5-8 set forth the recombinant plasmid vector, pSNAV1/HO-1. As shown in Figure 6 of the application as filed, pSNAV1/HO-1 comprises more than the AAV/HO-portion of the vector. In particular, pSNAV1/HO-1 also comprises an Amp^r, an SV40, and a Neo^r region which are not disclosed or suggested in Dzau. Thus, Dzau does not anticipate claims 1 and 5-8 because Dzau does not disclose all elements of pSNAV1/HO-1 claimed in 1, nor in claims 5-8 which depend there from.

Further, claim 11 has been amended to recite that administration of the viral vector is via *in situ* perfusion of an organ. Although Dzau discloses the administration of viral vectors containing the HO-1 gene to cells *in vitro* followed by introduction of the cells into a patient to treat cardiac disorders such as stroke, myocardial infraction, and congestive heart failure (*see* Dzau, *e.g.*, paragraphs [0011] and [0071]), Dzau neither describes nor suggests that an entire organ can be perfused *in situ* for the purposes of transplantation into an animal. Thus, Dzau does not disclose all the elements of claim 11.

Applicants further note that Dzau is misclassified as a 35 U.S.C. § 102(b) reference, since Dzau was published on January 30, 2003 and 35 U.S.C. § 102(b) references must be

published at least 1 year prior to the filing date of the present invention (*i.e.*, December 30, 2002). Accordingly, Dzau should instead be a 35 U.S.C. § 102(e) reference because Dzau is a U.S. published application filed in the U.S. before the filing date of the present application. Nonetheless, Applicants respectfully submit that the present invention is not anticipated by Dzau for at least those reasons stated above.

Applicants respectfully request that these rejections be withdrawn.

C. Coffin

Claims 2 and 3 stand rejected as anticipated under 35 U.S.C § 102(a) by Coffin et al. (U.S. Application Publication No. 2005/02006847) (Coffin) because claims 2 and 3 are drawn to any AAV vector cell strain or any AAV vector BHK-21 cell strain, respectively, and Coffin describes the same.

Applicants respectfully traverse these rejections.

Applicants submit that Coffin does not disclose or suggest all of the claim elements of amended claim 2. Applicants direct the Examiner's attention to amended claim 2, wherein the product-by-process claim language has been replaced with "comprising the recombinant plasmid vector of claim 1." In light of this amendment, Applicants submit that Coffin does not disclose an AAV vector cell strain comprising the recombinant plasmid vector pSNAV1/HO-1 and, therefore, does not anticipate claim 2, nor claim 3 dependent there from.

Applicants further note that Coffin is misclassified as 35 U.S.C. § 102(a) reference because this reference was not published until after filing date of the present application. Applicants submit that Coffin should instead be classified as a 35 U.S.C § 102(e) reference because Coffin is a U.S. published application filed in the U.S. before the filing date of the present application. Nonetheless, applicants respectfully submit that the present invention is not anticipated by Coffin for at least those reasons stated above.

Applicants respectfully request that these rejections be withdrawn.

VIII. Claim Rejections: Obviousness

Claims 1-10 stand rejected as obvious over Coffin in light of Dzau. The Examiner asserts that the present invention is obvious because it would have been obvious to a person skilled in the art to use the AAV vector containing the HO-1 gene under the control of a CMV promoter sequence as taught in Dzau with the process to manufacture a recombinant AAV/HO-1 virus using the recombinant HSV helper virus and BHK cells as described by Coffin.

Applicants respectfully traverse these rejections.

Applicants submit that obviousness can only be found when each element of the rejected claims is disclosed or suggested in the prior art references. Claims 1-10 each recite the plasmid vector, pSNAV1/HO-1 comprising an Amp^r, an SV40, and a Neo^r region, as an element. However, neither Dzau nor Coffin, alone or in combination, disclose or suggest a plasmid vector containing these regions comprising applicants' presently claimed invention. Accordingly, applicants submit that claims 1-10 are not obvious.

Applicants respectfully request that these rejections be withdrawn.

CONCLUSION

In view of the above amendments and remarks, applicants believe the pending application is in condition for allowance. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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